Spring 2019

ASSESSING FUNCTIONAL CONNECTIVITY OF THE NEURAL NETWORKS IN CHILDHOOD APRAXIA OF SPEECH USING RESTING STATE FMRI FOLLOWING THE TREATMENT FOR ESTABLISHING MOTOR PROGRAM ORGANIZATION (TEMPO)

Morgan James
University of New Hampshire, Durham

ASSESSING FUNCTIONAL CONNECTIVITY OF THE NEURAL NETWORKS IN CHILDHOOD APRAXIA OF SPEECH USING RESTING STATE FMRI FOLLOWING THE TREATMENT FOR ESTABLISHING MOTOR PROGRAM ORGANIZATION (TEMPO)

BY

MORGAN F. JAMES

B.S. Communication Sciences and Disorders; University of New Hampshire, 2017

THESIS

Submitted to the University of New Hampshire
in Partial Fulfillment of
the Requirements for the Degree of

Master of Science
in
Communication Sciences and Disorders

May, 2019

This thesis has been examined and approved in partial fulfillment of the requirements for the degree of Master's of Science in Communication Sciences and Disorders by:

Donald A. Robin, Ph.D.
Thesis Director, Professor & Chair
Communication Sciences & Disorders

Jenna L. Campbell, Ph.D.
Post-Doctoral Fellow
Communication Sciences & Disorders

Amy E. Ramage, Ph.D.
Assistant Professor
Communication Sciences & Disorders

Kirrie J. Ballard, Ph.D.
Professor of Speech Pathology
University of Sydney

On April 19, 2018

Original approval signatures are on file with the University of New Hampshire Graduate School.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

LIST OF FIGURES

ASSESSING FUNCTIONAL CONNECTIVITY OF THE NEURAL NETWORKS IN CHILDHOOD APRAXIA OF SPEECH USING RESTING STATE FMRI FOLLOWING THE TREATMENT FOR ESTABLISHING MOTOR PROGRAM ORGANIZATION (TEMPO)

by
Morgan James
University of New Hampshire, May, 2019

Childhood apraxia of speech (CAS) is a motor speech disorder characterized by segmentation (increased segment and intersegment duration), speech sound distortions and equal lexical stress. This study examined the effects of four weeks of Treatment for Establishing Motor Program Organization (TEMPO) in inducing experience-based changes in the brain. A fMRI resting state functional connectivity analysis was used in a single-subject pre- and post-TEMPO to quantify the changes associated with this treatment. Increases in connectivity strength between specific regions of the brain were observed, with the largest change in connectivity strength occurring between the left and right ventral premotor cortex (vPMC). These regions are known to be involved in speech motor programming. These results demonstrate the efficacy of TEMPO in inducing experience-based neural plastic changes, as well as provide the first data supporting the involvement of the left ventral premotor cortex in CAS.

Introduction

Childhood Apraxia of Speech (CAS) is an impairment in the programming and realization of intact motor units of speech (American Speech-Language-Hearing Association [ASHA], 2007; McNeil, Robin & Schmidt, 2009). Differential diagnosis of apraxia of speech is based on perceptual judgment of specific speech symptoms in the absence of fundamental neuromuscular, cognitive or linguistic impairments (McNeil et al., 2011). There are three core symptoms used to differentiate apraxia of speech from other speech sound disorders: a) prolongation of speech sounds including increase in segment and intersegment duration, b) inconsistent distortion of speech sounds, with consistency in distortion type, c) and abnormal prosody, characterized by inappropriate stressing of syllables and sounds (Murray, McCabe & Ballard, 2015).

CAS is a debilitating condition affecting the development of intelligible speech, causing deficits in social and academic growth (Sylvestre et al., 2013). When left untreated, CAS has been shown to persist into adulthood and lead to reduced career options, social interactions and increased rates of depression compared to the typical population (McCabe et al., 2017; Carigg et al. 2015; Lewis et al. 2004). Critically, the majority of treatments to date have not been structured within a motor learning framework limiting their potential success (Strand, Stoeckel, & Baas, 2006). Principles of Motor Learning (PML) can be used as a guideline for designing effective interventions in motor speech disorders (Maas et al., 2008). PML were explained by Schmidt within the context of the Schema Theory of Motor Control and Learning (1975). Motor Learning involves structuring practice and feedback conditions to promote relatively permanent changes in the capacity for developing skilled actions (Schmidt, & Lee, 2005). For example, these principles include conditions that describe practice amount, its variability, as well as the timing and frequency of feedback (Maas et al., 2008).

It is also known that the brain changes based on one's experiences. This result is known as experience-based neural plasticity. Neural plasticity is the ability of the brain to change and adapt in response to environmental cues, experience and behavior (Ludlow et al., 2008). Effective speech treatment may serve as an example of an experience that results in neural plastic changes in the brain. Experience-based neural plasticity is driven and shaped by a number of principles including specificity, age, acuity, salience and intensity (Kleim & Jones, 2008). Other specific principles center around the idea of "use it or lose it" and "use it and improve it" which reflect the idea that when a neural connection or pathway is not used, it will begin to degrade, and conversely, if a pathway is engaged through positive adaptive practice and use, the connection will grow stronger. At a system level, the strength of network connectivity can be quantified using functional magnetic resonance imaging.

The appropriate experiences result in changes in the brain, either by recruiting residual substrates to perform the impaired function, or by producing neuronal sprouting and dendritic growth (Saur et al., 2006). Therefore, it is critical for a speech treatment to target these principles of experience-based neural plasticity in order to maximize treatment potential and personal communication. Further, the development of treatments for CAS, a motor speech disorder, must be consistent with Principles of Motor Learning and those that drive neural plasticity.

One approach to treating children with CAS is called Treatment for Establishing Motor Program Organization (TEMPO). TEMPO was developed based on PML, and was designed to engage experience-based neural plasticity, in order to target the three core features of CAS, that are a) prolongation of speech sounds including increase in segment and intersegment duration, b) distortion of speech sounds, c) and abnormal prosody, characterized by inappropriate stressing of syllables and sounds (McNeil, Robin & Schmidt, 2009

). In brief, TEMPO was designed to be intensive (four one-hour sessions per week for four weeks) and to incorporate high numbers of repetition with a 60% rate of feedback in order to maximize the potential for functional change to take place. The preliminary behavioral data for TEMPO have demonstrated moderate to strong effect sizes (Miller et al., 2018), but its effects on neural plasticity are still unknown, hampering the ability to optimize the treatment's effect on neuralplasticity.

Currently, there is limited research investigating the neurologic basis of CAS. Studies have proposed changes in cortical thickness (Liegeois, Mayes & Morgan, 2014) as well as general functional anomalies at the metabolic or neurotransmitter level (Legeois & Morgan, 2012) as possible underlying causes or biomarkers. However, more research has been conducted in stroke-induced apraxia of speech (AOS), which has led to the current understanding that it is subsequent to damage in the left inferior frontal cortex, specifically the left ventral premotor cortex (left vPMc) (Robin et al., 2008; Ziegler, 2008; Duffy, 2013; Ballard et al., 2014) and its functional connectivity with right ventral premotor cortex (right vPMC) and right anterior insula (raINS) (New et al., 2015). Although CAS occurs in childhood and AOS occurs from known neurological damage later in life, both share the common core symptoms (Shriberg, Lohmeier, Strand & Jakielski, 2012) and many believe them to arise from the same underlying neural substrates (McNeil et al., 2009).

Finally, CAS and AOS can be understood within the broad framework of the Directions into Velocities of Articulators (DIVA) model of motor speech control (Guenther et al., 1998; Guenther, 2006, 2016; Guenther and Vladusich, 2012; Ballard et al., 2018). DIVA provides a computationally and neuro-anatomically explicit account of the network of brain regions involved in speech acquisition and production (Tourville & Guenther, 2011; Guenther, 2016). The model is based on the principle that articulatory movements involve the precise integration

of feedback and forward control systems, with feedback coming from the auditory and somatosensory subsystem loops. A critical part of this model has been the mapping of each system component onto neural substrates or regions which permits the simulation of various speech disorders. Within DIVA, the left ventral premotor cortex (left vPMC) is associated with the "speech sound map", or the section of the model that is crucial for the readout of frequently used speech motor programs belonging to the speaker's native language. This section of the model has been theorized as the area of dysfunction in AOS, as it reflects the research supporting CAS and AOS as a disruption of the feedforward network, and the left vPMC, within DIVA is a key area that is necessary for feedforward processing (Ballard et al., 2018; Tourville, 2011; Maas, 2015). In addition to postulating individual brain regions as potential sites for damage, researchers have begun to consider the idea of studying a network of regions associated with AOS/CAS and corresponding to the DIVA model, in the hopes that it will be more representative and elucidating of the entire network's function.

One way to understand the neural basis of CAS as well as how TEMPO would induce experience-based neural plasticity is to use resting state functional MRI (rsfMRI). Resting state analysis, allows for the investigation of the relationship of brain regions independent of task performance. Moreover, rsfMRI is obtained when a subject is lying in the scanner in a task-free environment, and yet still reflects the majority of networks found during task performance (Smith et al., 2011). Finally, it is thought that rsfMRI networks represent more permanent brain states than those elicited by performance-based tasks during scanning, meaning they are the ideal targets for assessing neuroplasticity as they are longer lasting over time (van den Heuvel and Hulshoff, 2010; New et al., 2015).

In order to gain insight into the neural mechanisms underlying CAS, New et al. (2015) conducted a rsfMRI study investigating the differences in network connectivity between three

groups, categorized as stroke with AOS, stroke without AOS, and healthy controls. The regions of interest in that study included coordinates that have been identified by meta-analyses of speech (Eickhoff et al., 2009; Guenther, 2016). Specifically, the purpose was to test the three brain regions hypothesized by others (Nielson, 1936; Wertz et al., 1984; Trupe et al., 2013; Dronkers, 1996; Ogar et al., 2006; Hillis et al., 2004; Graff-Radfor et al., 2014; Robin et al., 2008) to be responsible for apraxia of speech when lesioned. These areas include: a) left interior frontal gyrus (IFG) (BA 44) b) left anterior insula (laINS) and c) left ventral premotor cortex (lvPM) (BA6). The study also included the homologous regions in the right hemisphere in order to further delineate potential network impairments, as well as provide information about the role of the right-sided regions following stroke.

Results of the New et al. study revealed reduced functional connectivity of the bilateral PM seeds in participants with AOS compared to AOS-absent and healthy controls (New et al., 2015). In addition, a negative relationship was observed between the left PMC and right aINS, potentially indicating the role of the right aINS in compensating for the left PMC damage. Connectivity strength was also found to correlate negatively with apraxia severity. Both of these findings support the role of the left PMC region in the pathogenesis of apraxia of speech (New et al., 2015). As outlined above, New et al. provided evidence that AOS and CAS stem from the same underlying mechanism. Therefore, it makes sense that the neural basis of the two disorders is similar, and using the coordinates (specific areas mapped out in the brain) reported by New et al., (2015) is justified.

Importantly, there are few neural imaging data on children with CAS and, to our knowledge, none pre- and post-treatment. Therefore, the purpose of the current study was to collect brain imaging data in one child with apraxia of speech before and after TEMPO. Perceptual and acoustic measures of speech were also collected. This approach allowed for

gaining knowledge of functional connectivity in the subject associated with CAS and determining how that functional connectivity changed as a function of treatment with TEMPO.

In summary, the purpose of this proof-of-principle experiment was to examine if TEMPO induces changes in experience-based neural plasticity by quantifying functional connectivity of the brain during resting state functional magnetic resonance imaging (rsfMRI) immediately pre- and post-treatment. Specifically, it was predicted that the predominant changes induced by TEMPO would be between left and right premotor cortex. The hypothesized regions of interest emerged because of several prominent findings in the New et al. study. First, the patient group (those with AOS and those who suffered stroke without AOS (non-AOS)) were found to have weaker connectivity strength between all bilateral seeds when than compared to healthy controls. Second, further delineation of connectivity strength revealed that the AOS and non-AOS patient groups demonstrated differing patterns of connectivity between the lvPM and rvPM as well as lvPM and raINS. The final evidence in support of this hypothesis was that the severity of apraxia of speech correlated significantly with lvPM and rvPM, whereas laINS and raINS connectivity was associated with nonverbal oral apraxia, and not apraxia of speech.

Based on these findings of New et al., the primary hypothesis of this work is that there will be changes in brain connectivity between left and right premotor cortex and between left premotor cortex and right anterior insula associated with TEMPO treatment in children with CAS.

Methods

Participant SC

The participant in this study was a 7-year-old male who was part of a larger study examining the behavioral effects of TEMPO in children with CAS aged 4-12 years (Miller et al., 2018). The participant met the inclusion criteria for that study which included: a diagnosis of

CAS, absence of muscular and structural abnormalities, muscle weakness or altered tone/reflex, and absence of developmental, neurological, genetic conditions or speech disorders (other than confirmed CAS), native English speaker, functional hearing, and near normal receptive and expressive language skills to understand task instructions and requirements in the treatment program. To confirm functional hearing, the participant was given a pure tone hearing screen and passed at 25 dB for 500, 1000, 2000 and 4000 Hz in both ears. Muscle weakness and tone were assessed with the Motor Speech Examination (Duffy, 2003), in which the participant was found to perform within normal limits for all non-speech tasks and demonstrated evidence of all three CAS core characteristics on the speech tasks. An absence of any co-occurring developmental condition was ruled out during parent interview. The diagnosis of CAS was made by unanimous agreement amongst experienced members of the research team (Robin, Ballard) during the speech tasks of the Motor Speech Examination (Duffy, 2013). Speech features observed during the Motor Speech Examination included the three key features of CAS, which are: increased segment and intersegment durations, distortion of speech sounds and inappropriate lexical stress.

In order to characterize the participant's language ability and rule out the presence of any co-occurring language deficit, the participant was administered the Clinical Evaluation of Language Fundamentals- Fifth Edition. (CELF-5; Wiig, Semel, & Secord, 2013) (see Table 1). The mean score for both the receptive and expressive language index is 100 (+/- 1 SD, 85-115). The participant scored 80 for both subtests, 1.33 SD below the mean. This score indicates a marginal or mild low average severity. However, the participant scored in the average range for 4 out of the 6 subtests, one of which being sentence comprehension, so it was decided by the investigation team that average sentence comprehension and absence of any developmental diagnosis indicated adequate receptive language to participate in the treatment program.

Table 1. Participant characteristics

Participant	Age (year;month)	Sex	Treatment Level (syllables)	Number of Baselines	CELF-5	Receptive Index Score	Expressive Index Score	Core Language Score	Language Content Index
1	7;10	M	3	3		80	89	87	80

Treatment Paradigm

Stimuli

This treatment paradigm was adapted from the larger group study completed in 2018 by Miller and colleagues. Treatment and experimental probe lists consisted of three-syllable pseudowords with either a strong-weak (SW; e.g., TAgibu) or weak-strong (WS; e.g., giTAbu) stress pattern over the first two syllables (see Ballard et al., 2010). A list of 72 possible CVCVCV combinations containing three different plosive consonants (/b/, /t/, and /g/) and three different long vowels (/a/, /i/, /u/) was generated, in both SW and WS stress conditions. Of those, 20 syllable strings were randomly selected for treatment (Set 1) in both SW and WS stress conditions. The remaining 18 combinations were left untreated (Set 2) to measure transfer to similar but untreated exemplars of both stress conditions.

Experimental Design

Our participant completed two baseline tests to measure pre-treatment performance on each of the stimulus sets. Additional experimental probes were completed during the treatment period, immediately post-treatment, and at one-month post-treatment to measure treatment effects, generalization to untreated items, and retention. Baseline and post-treatment probes contained a total of 120 items, including 20 items (10 SW and 10 WS) randomly selected from Set 1 and Set 2, as well as similar fricative pseudo-words, real words containing treated sounds, and a set of more and less complex pseudo-word stimuli (four-syllable versus three-syllable

targets). Only data from Set 1 and Set 2 are reported here. Stimuli were presented in one of ten randomly selected carrier phrases (eg. “There’s my ____” “It’s a red____).

Baseline probes were scheduled such that the last one was completed about one week before the beginning of the first treatment session. The first post-treatment probe was completed within three days of ending treatment. The second was completed approximately one-month post-treatment to measure retention of any treatment effect. The participant did not receive any speech therapy during the one-month retention phase. The author administered all treatment and all baseline and experimental post-treatment probes, with the exception of one baseline, which was completed by another clinician.

Treatment

Treatment sessions were conducted on four consecutive days a week in 60-min sessions for a four-week period. The author, a student clinician, was the primary clinician for the participant. A minimum of 25% of the child’s sessions were observed by a certified Speech-Language Pathologist and recordings of sessions were also observed by a second investigator (AP) on this project to measure treatment fidelity.

Intervention explicitly targeted each of the three features of CAS through repeated productions of the multisyllabic pseudo-words (e.g. taBIgu) at a natural speech rate, where correct production was assessed as having correct sound production, fluent transitions between syllables and accurate lexical stress. Twenty stimuli (10 SW and 10 WS) from Set 1 were randomly selected for practice in each session. Treatment was structured within a motor learning framework (Schmidt & Lee, 2005; Maas, Robin, Austermann Hula et al., 2008). That is, each treatment session consisted of (1) Pre-Practice, continuing until the child correctly produced five stimuli with clinician-provided Knowledge of Performance (KP) feedback and cues as necessary; and (2) Practice, consisting of 100 total productions of the twenty randomly ordered stimuli (see

Ballard et al., 2010). The Practice stage adhered to a strict low frequency, delayed feedback schedule with only Knowledge of Results (KR) feedback provided on 60% of trials after a 3-second delay. Clinicians used a feedback sheet containing a visual of the three targeted features (sounds, stress, segmentation) during Pre-Practice and Practice to refer to each term as they gave feedback (e.g. "Nice and smooth but sounds and stress weren't right.") There was also a 5-second delay following feedback before presentation of the next stimulus.

For the first two sessions, the participant completed an hour of Pre-Practice to train and understand the expectations for an accurate production. In subsequent sessions, Pre-Practice lasted no more than 15 minutes. Stimuli were presented auditorily by the clinician, with a 3 second delay between the model and the child's production.

Equipment

All experimental probes and treatment sessions were recorded in a quiet room at 44.1 kHz with Samson XPD1 microphones, positioned 15 cm for the child's mouth.

Acoustic Analysis

Acoustic analyses were completed by the author with support from an acoustically-trained research assistant using Praat signal-processing software (Boersma & Weenik, 2001). Lexical stress was measured through comparison of vowel duration (ms) of strong and weak syllables in treated and untreated plosive stimuli on pre- and post-treatment experimental probes. Vowel duration was measured between the first and last glottal pulse of the vocalic nucleus, as indicated by energy extending through F1 and F2 displayed on the wideband spectrogram, and using fundamental frequency, formant, and intensity contours generated by the Praat software (Ballard et al., 2010, Kent & Read, 1992).

The pairwise variability index (PVI) of each variable was calculated using Equation 1 to provide a normalized comparison of the strong and weak syllable in each stimulus:

$$PVI = 100 \times [d_k - d_{k+1})/[(d_k + d_{k+1})/2], \quad (1)$$

where d is the duration of the k^{th} syllable (Ballard et al., 2010; Low, Grabe, & Nolan, 2000). A higher PVI value reflects increased contrast in lexical stress, whereas a PVI of zero indicates equal stress across syllables.

PVI was only calculated for stimuli in which no syllables were omitted, and both strong and weak syllables had a measurable vowel (i.e. not whispered). Stimuli in which the child did not repeat the intended stress target (i.e. produced a WS pseudoword instead of SW) were also excluded from analysis.

Segmentation was measured as intersegment duration, or the amount of time between syllables. This was defined as the time from the last glottal pulse in a syllable, as indicated by the end of F1 and F2 in the wideband spectrogram, to the onset of the plosive burst in the following syllable. For items in which the child added an extra syllable, only the syllables that best fit the intended stress pattern were included for analysis. Due to either omission or severe distortion of the plosive consonant, it was not possible to distinguish start and end points of segments for 0.03% of stimulus items. Thus, the ISD was not measurable for a total of 13 out of 414 data points.

Perceptual Analysis

Stimuli that were eligible for acoustic analysis also underwent perceptual analysis which was completed by the author and the committee chair (DR). For items with disagreements, consensus was reached through discussion. Stimuli were perceptually judged on each of the CAS core characteristics which include: stress, segmentation and distortions. A unique scoring system was devised for each feature, the criteria for which are as follows:

Segmentation was scored using a 5-point scale where a 1 indicated smooth, connected syllables matching the clinician's model, and a 5 was heavily segmented. The goal when scoring

smoothness was to grade according to the overall impression for the whole pseudo-word. For example, if the intersegment duration between the first two syllables was a 1, but the segment duration of the last syllable was a 5, a score of 3 was assigned based on the average or overall impression of smoothness.

Distortions were scored based on the number of syllables in a stimulus containing a distorted consonant (3 or 4 depending on the stimuli), and a percent correct was calculated per word. We chose to score consonants as opposed to all sounds because consonants were directly targeted for non-distorted production while vowels were targeted more for lexical stress. Errors other than distortions such as substitutions, omissions and transpositions were noted but not counted as they are not errors specifically characteristic of apraxia. If a substituted or transposed sound was distorted, however, that was then counted towards the overall distortion score.

Finally, syllable stress was also rated on a 5-point scale where a 1 indicated a clear SW stress pattern, a 5 indicated a clear WS stress pattern, and a 3 indicated equal stress on the first two syllables (with a 2 or 4 trending in either direction). If the participant omitted either of the first two syllables, the stimulus was not scored for that criterion.

MRI data acquisition

Resting state functional magnetic resonance imaging (fMRI) was completed on a MAGNETOM Prisma 3-Tesla Siemens fMRI scanner (Siemens Medical Solutions USA, Malvern, PA) using a 32-channel head coil system. Scanning took place at both pre-treatment and post-treatment time points. The pre-treatment scan was taken 4 days prior to the start of treatment, and the post-treatment scan was taken the next day following the end treatment. Functional, resting state images were acquired using the following parameters: a) 54 slices, b) voxel size = 3.0 x 3.0 x 3.0 mm, c) 255 images, d) TR/TE = 2000/30 ms, e) flip angle = 65°, f) FOV = 240 mm, g) matrix = 80 x 80, h) motion correction = OFF. The functional scan lasted 8

minutes and 37 seconds. Next, a high-resolution T1-weighted MPRAGE whole-brain scan was acquired for spatial normalization of the functional images. Prior to initiation of the scan session, the participant was allowed time to familiarize and become comfortable with the machine. He was given instructions by the Research Coordinator to lay still with his eyes open, fixated on the cross above him. In addition, the participant was given ear muffs and padding around the head for hearing protection and to provide comfort. The participant's parent was also allowed to enter the scan room to provide comfort and reminders to remain still. Both the child and his parent were screened for metal prior to entering the scan room in accordance with IRB protocol.

ROI selection

Functional connectivity was assessed by selecting and analyzing cortical regions of interest hypothesized to play a role in AOS. The specific coordinates and regions were selected from the 2015 study conducted by New and colleagues which include: left inferior frontal gyrus (lIFG), left anterior insula (laINS) and the left ventral premotor cortex (lvPMC) (see Table 2 for details). Bilateral correlates for the aforementioned regions were also included for a few primary reasons. First, bilateral regions were assessed in order to determine whether homolog regions were connected in our participant, as seen in typically developing children (Emerson, Gao & Lin, 2016). Second, the rvPMC was specifically included due to its known involvement in speech processing and its probable role in the larger speech motor network (Guenther, 2006).

Table 2. Regions of Interest

Region of Interest	MNI Coordinates		
	X	Y	Z
Left inferior frontal gyrus (BA44) (lIFG)	-50	10	5
Left inferior frontal gyrus (rIFG)	50	10	5
Left anterior insula (laINS)	-32	15	2
Right anterior insula (raINS)	32	15	2
Left ventral premotor cortex (BA6) (lPM)	-58	1	23
Right ventral premotor cortex (rPM)	58	1	23

Data Analysis

Data were analyzed with functional connectivity metrics, using Statistical Parametric Mapping, version 12 software (SPM12, http://www.fil.ion.ucl.ac.uk/sp m/software/spm12/) run through Matlab 9.3 (R2017b). Response Exploration for Neuroimaging Datasets (REX, https://www.ncbi.nlm.nih.gov/pubmed/17985253) was used to extract the time series. SPM12 was used to spatially normalize the structural T1 scan to standard MNI space. All normalized images were then smoothed with an isotropic kernel of 9mm. Multi-Image Analysis GUI (Mango, http://ric.uthscsa.edu/) was used to create a 3D brain image after the functional connectivity metrics were applied. This adapted protocol has been completed successfully in the previously mentioned study conducted by New et al., in a group of patients classified as having AOS or AOS-absent following stroke (2015).

Imaging analyses

The time course for each ROI was extracted as the first eigenvariate of the resting-state signal time-series of all grey-matter voxels located within 5mm of the respective peak coordinate. To measure functional connectivity, linear Pearson correlation coefficients were computed between the extracted time series of each of the seed regions. These voxel-wise correlation coefficients were then converted to Fisher's Z-values representing the functional connectivity strength for each connection in the model. Network models of connectivity were analyzed pre- and post-treatment.

Important Connections

This is a descriptive study on a single-subject, where qualitative decisions were made during the selection of important connections. As a measure of functional connectivity strength, Pearson correlation coefficients (r) were calculated for each connection among the regions proposed to have involvement New et al. (2015), by correlating the extracted time series for each seed (bilateral: ventral premotor cortex (vPM), anterior insula (aINS) and inferior frontal gyrus

(IFG)). Correlations were then converted into Fisher z-scores for the functional connectivity analysis, as done in New et al. (2015). Table 3 displays both R-values and z-scores for all connections in which a resting state connectivity analysis was completed. Connections were important if they reached an R-value score of greater than 0.5 at the post-treatment time point. These significant connections were then calculated and reported as fisher z-scores (Figure 5). There are several connections we do not report that also demonstrate strong effect sizes, however, these connections remain stable pre-treatment compared to post-treatment, therefore they do not appear to be influenced by treatment. Thus, considering the goal of this study is to investigate how TEMPO induces experience-based changes in neural plasticity, we are only reporting those changed scores.

Results

Behavioral Data

Acoustic Data

Results from this study's behavioral data analysis parallel those from a larger group study (n=12) (Miller et al., 2018). Specifically, phase analysis for intersegment duration revealed a significant effect due to phase, $F(2, 401) = 16.32$, $p < 0.001$, eta-squared 0.077 = medium to large effect size. Means for each treatment phase are plotted in Figure 1. Main effect of set was not significant in describing the variance of our dependent variable which indicates a generalizability effect of the treatment.

A significant effect due to phase and set was seen for WS stimuli $F(4, 95) = 2.77$, $p < 0.05$, eta-squared 0.114 = large effect, while no significant change was seen for the SW stimuli $F(4, 102) = 0.447$, $p > 0.05$. Means for each treatment phase are plotted in Figure 2.

Figure 1. Intersegment duration means plotted by treatment phase.

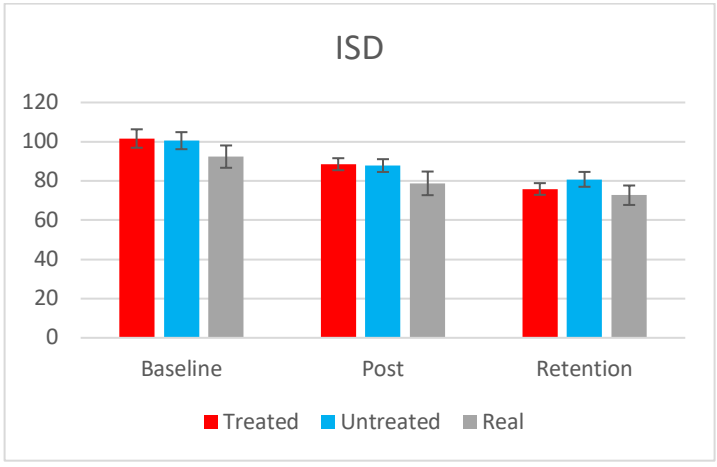
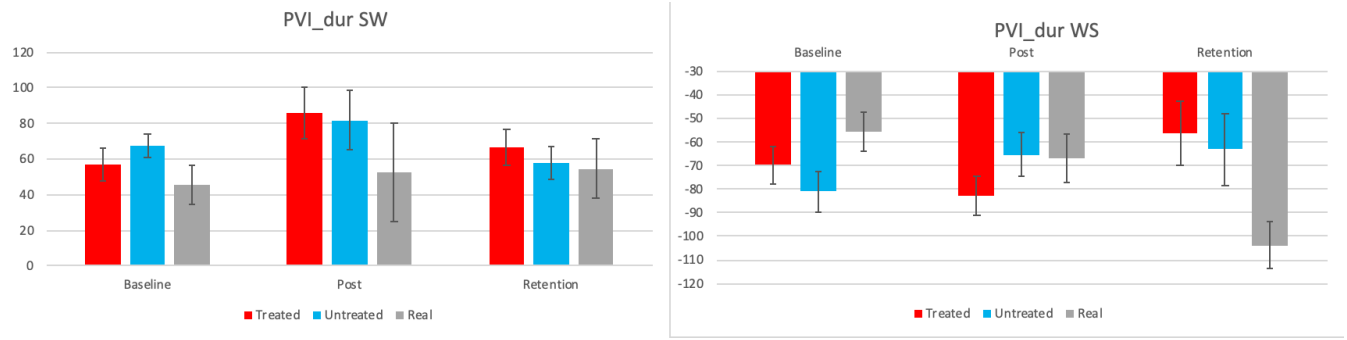


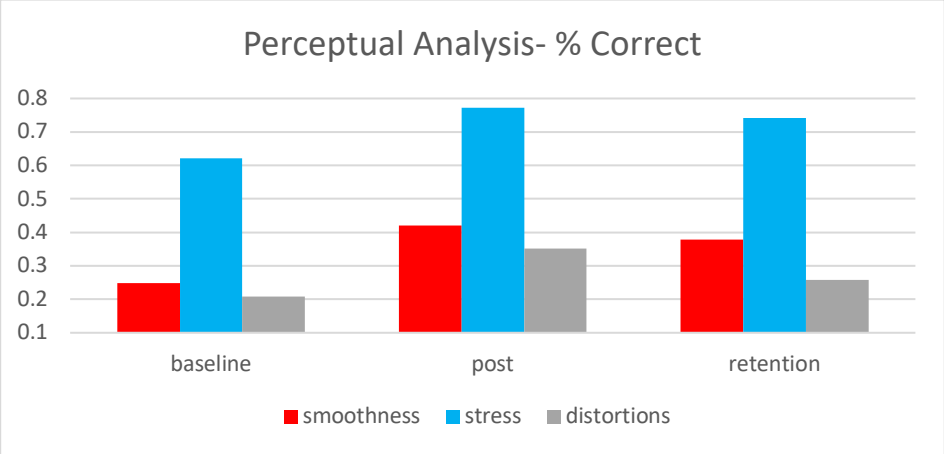
Figure 2. PVI means plotted by treatment phase.



Perceptual Data

Significance for perceptual analysis was determined by calculating the percent correct of each feature (segmentation, distortions, stress) and comparing them at each time point. The results from this study paralleled those from the aforementioned larger group study (n=12) (Miller et al., 2018). Percent correct improved from baseline to post-treatment probe in each feature. A maintenance effect was also seen during comparison of baseline to the retention probe 3-months post treatment. Results from this study are plotted in Figure 3.

Figure 3. Percent correct of analyzed perceptual features by phase.



Imaging Data

Strong connectivity was observed between all bilateral connections. A substantial relationship was also seen between the rvPM and laINS. Out of the three bilateral connections observed, the greatest change in connectivity strength was seen between the lvPM and rvPM. (See Table 3).

Table 3. Correlation metrics for the functional connectivity analysis where (a) is correlation pre-treatment and (b) is correlation post-treatment. Connections marked with an asterisk indicate those that demonstrated a weak connection pre-treatment that increased to a strong connection at post-treatment.

Connection	Pearson's R	Connection Strength (Fisher's Z)
rvPM-rIFG	0.22	0.23
rvPM-raINS	0.27	0.27
rvPM-lvPM*	0.19*	0.19*
rvPM-lIFG	0.45	0.48
rvPM-laINS	0.57	0.64
rIFG-raINS	0.86	1.29
rIFG-lvPM	0.18	0.18
rIFG-lIFG*	0.19*	0.20*
rIFG-laINS	0.43	0.45
raINS-lvPM	0.16	0.16
raINS-lIFG	0.27	0.28
raINS-laINS*	0.49*	0.53*
lvPM-lIFG	0.16	0.16
LvPM-laINS	0.15	0.15
lIFG-laINS	0.72	0.9

a. Pre-Treatment

Connection	Pearson's R	Connection Strength (Fisher's Z)
rvPM-rIFG	0.19	0.19
rvPM-raINS	0.05	0.05
rvPM-lvPM*	0.66*	0.73*
rvPM-lIFG	0.31	0.32
rvPM-laINS	0.21	0.22
rIFG-raINS	0.88	1.38
rIFG-lvPM	0.19	0.21
rIFG-lIFG*	0.55*	0.61*
rIFG-laINS	0.65	0.77
raINS-lvPM	0.18	0.18
raINS-lIFG	0.50	0.55
raINS-laINS*	0.73*	0.94*
lvPM-lIFG	0.32	0.33
LvPM-laINS	0.35	0.37
lIFG-laINS	0.8	1.11

b. Post-Treatment

Figure 4a. Significant changes in functional connectivity where (a) is pre-treatment and (b) is post-treatment displayed using bolded lines with z-score indicating connectivity strength on model brain.

a. Pre-Treatment

b. Post-Treatment

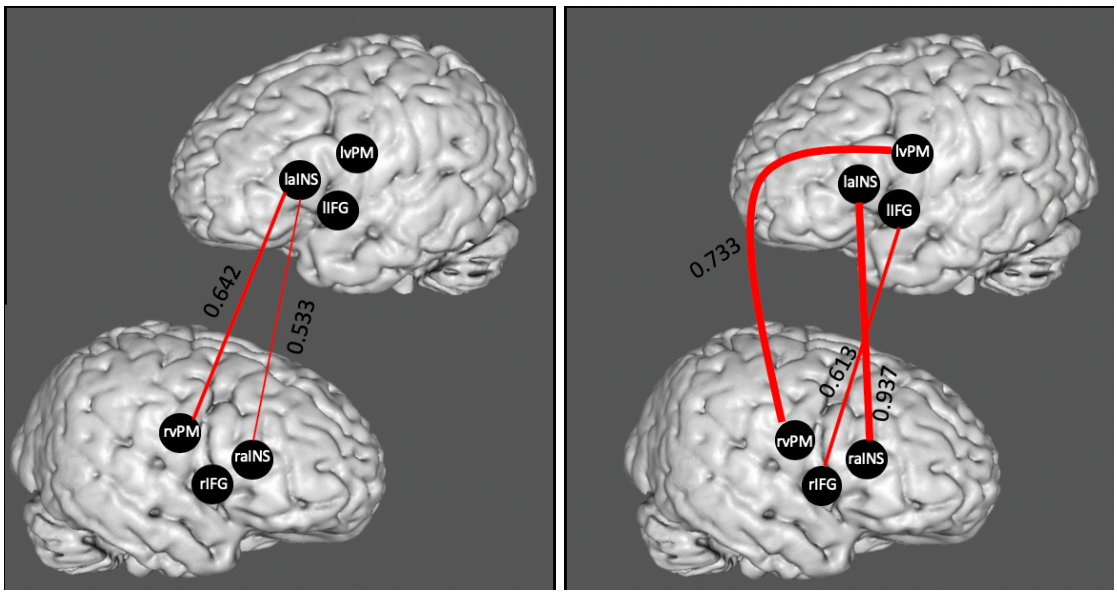
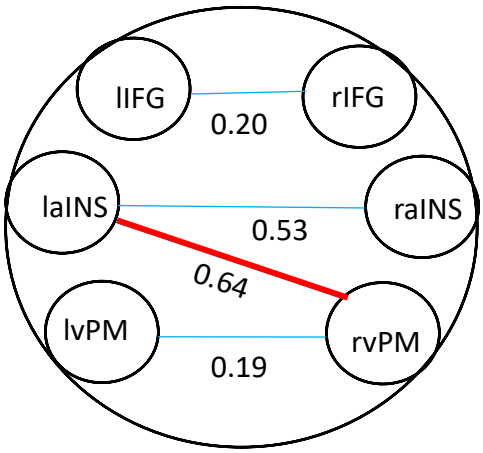
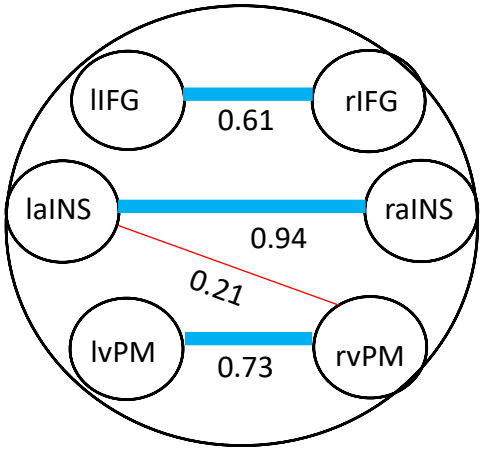


Figure 4b. Important changes in functional connectivity where (a) is pre-treatment and (b) is post-treatment displayed using bolded lines with z-score indicating connectivity strength on circle diagram

a. Pre-Treatment



b. Post-Treatment



Discussion

It is critical to understand the role experience-based neural plasticity in treatment important to the underlying mechanism in order to ensure effective, specific, and long-lasting changes in behavior. Therefore, this study aimed to investigate the effects of a new treatment for CAS, called TEMPO, in inducing changes in brain networks. This was done in a single subject by quantifying functional connectivity during resting state fMRI. All behavioral data that emerged from the TEMPO treatment were analyzed acoustically and perceptually as done in previous work (Miller et al., 2018). This approach allowed for interpretation of potential interpret brain changes associated with successful implementation of the treatment.

The key behavioral findings of the study were that positive changes in acoustic and perceptual measures of speech paralleled those in the larger group study (Miller et al., 2018). Specifically, all three key features of CAS improved with treatment. Acoustically, we found reduced intersegment durations and increased PVI for SW and WS treated stimuli sets post-

treatment compared to pre-treatment. In regard to region of interest selection in the brain, we selected three regions on the left and their homologs on the right which were: lvPM and rvPM, laINS and raINS, lIFG and rIFG. Each hypothesis is addressed below.

Development in Homologous Brain Connectivity

In typical development, at rest, it is expected to see homologous regions in the left and right hemisphere functionally connected to one another (Emerson, Gao & Lin, 2016). Prior to the start of treatment, none of our bilateral regions of interest demonstrated strong homologous connectivity. Following treatment, however, all of the observed bilateral regions increased to a strong level of connectivity (Pearson's r, reported in Fisher Z). Importantly, this suggests a move towards normal brain function following treatment. Firstly, the realignment of general homologous regions to be more bilaterally connected is representative of typically developing children, as seen in our study (Emerson et al., 2016). Secondly, fMRI studies investigating emerging language in children have found that the language system, specifically, is more bilaterally organized than in its adult form (Emerson, Gao & Lin, 2016; Dehaene-Lambertz et al., 2002; Perani et al., 2011; Sato et al., 2012; Shultz et al., 2014). Therefore, our subject displayed a more normalized pattern of functional connectivity than he did prior to treatment.

Alternatively, the laINS and rvPM showed decreased connectivity strength associated with treatment, suggesting more normal pattern of brain function.

The Critical Role of the lvPM and rvPM Connectivity

The specific hypothesis in this study was that the predominant changes induced by TEMPO would be between lvPM and rvPM. In New et al., (2015), the prominent finding was that the AOS and non-AOS patient group demonstrated similar connectivity strength between the lvPM and raINS, while the AOS group had significantly reduced connectivity between lvPM and rvPM than compared to the non-AOS group. While both connections were reduced in both AOS and

non-AOS in comparison to the healthy controls, it was the connection between the lvPM and rvPM that was specific to the AOS group. Further, New et al. (2015) found that the connectivity strength between the lvPM and rvPM negatively correlated with apraxia severity, further providing evidence of the importance of this connection in apraxia of AOS. Recent analyses of these same data using causal modeling showed that the lvPM modulation of rvPM region differentiated apraxia from non-apraxia compared to healthy controls (Van De Water, 2019).

The lvPM and rvPM connection can also be explained within the DIVA model of speech. As previously mentioned, the DIVA model provides a unified and quantitative account of a wide range of speech production phenomena and neuroimaging data (Guenther, 2006; Guenther et al., 2006; Tourville and Guenther, 2011). Each module in the model has a hypothesized link to a specific neuroanatomic region based on previous human clinical and neuroimaging studies. In the DIVA model, the left ventral premotor cortex is predicted to play a role in the feedforward process associated with motor programming. In TEMPO, treatment was structured to bolster the INT subprocess of motor programming, which is the organizing of the internal structure of a unit by integrating various movement components into a coherent structure and loads the unit into a motor buffer until the time of initiation (Klapp, 1995, 2003; Maas, 2006). This INT process can be translated as the feedforward process in DIVA, which within the network is referred to as the speech sound map (lvPMC). The speech sound map in DIVA is likely responsible for similar processes as the INT subprocess in the model proposed by Klapp (1995, 2003), which is the motor programming, or "read out" of individual units of speech and the concatenation of those single unsegmented speech programs.

The data found here in CAS, support the use of DIVA relative to explaining various speech disorders. For example, DIVA has been used to simulate apraxia of speech and experimented by disrupting the speech sound map (Ames, 2009). The synthesized speech output in this case

presented with speech features consistent with apraxia of speech, including: phonemic distortions, schwa insertion, movement of syllable boundaries, vowel prolongations, and related prosodic alterations (McNeil et al., 2009, Ames, 2009, Ballard et al., 2014). In this same study, damage to the inferior frontal sulcus, however, did not appear to produce apraxic speech in this same manner, nor did it produce as many speech errors at the single word level, most of which were related to sequencing (a feature not characteristic of apraxia). Findings here may help further refine DIVA in the future by supporting the evidence of the left vPMC's role as the speech sound map, as while as the DIVA model's overall ability to inform disorders of speech.

Other Connectivity Changes in the Brain

As mentioned above, all of the bilateral connections observed in our study reached a Pearson's r of greater than 0.5. However, the connection with the greatest change in connectivity strength was the lvPM and rvPM. The lvPM and rvPM connection demonstrated an increase of $z = 0.5428$, while the bilateral aINS connection increased by $z = 0.404$ and the bilateral IFG connection increased by $z = 0.411$. This finding indicates that when targeting the three core features of apraxia of speech in this individual, per the TEMPO treatment, the lvPM and rvPM connection was the one most susceptible to change. Therefore, the result of this hypothesis is in support of those findings in both New et al. (2015) and DIVA (Guenther, 2006), that the lvPM and rvPM connection, but specifically the lvPM is the driving region of disruption in both adult acquired apraxia of speech and childhood apraxia of speech.

In DIVA, the lIFG is hypothesized as the phonological content buffer, which is responsible for the temporary storage of phonological units in an upcoming utterance (Guenther, 2006). The area in the model acts as a working memory buffer for the encoding and queuing of phonemes to be produced (Myers et al., 2009). It is an essential part of an efficient speech production model, and therefore makes sense that it too would improve and normalize with treatment.

The role of the left and right aINS in speech production is less clear. Several studies have investigated the role of various portions of the left insula and have found involvement in multiple aspects of both speech and language (Ackerman & Riecker, 2010; Oh et al., 2014). Given the general nature of the insula's involvement, it is also reasonable to assume its connectivity strength would increase following a motor speech treatment. However, there is no evidence to suggest that the anterior insula plays an explicit role in apraxia of speech.

Limitations

There are several limitations to this study. First, this was a single-case report, limiting the ability to generalize these results to other subjects. However, the preliminary data provides sufficient evidence that future studies should replicate these methods in a larger sample to determine group significances with more measurable effect sizes.

Second, this study should be replicated with a larger sample such that the behavioral metrics from treatment could be correlated with imaging results. Due to the nature of this single-case report, we were unable to make associations between the improvement of specific behavioral measure with specific regions of interest.

Lastly, this study only seeded and observed six regions out of a potentially much larger network related to speech motor programming and apraxia of speech, specifically. Future studies should also consider investigating other regions supported by the literature and theorized models to potentially play a role in AOS/CAS.

Conclusion

TEMPO induced experience-dependent neural plasticity in all observed bilateral seeds, signifying an assimilation of this subject's neural network to that of a typically developing peer. The greatest change in connectivity strength was observed between the left ventral premotor cortex and right ventral premotor cortex. This provides important evidence in the consensus that,

specifically, the left ventral premotor cortex is the driving region associated with apraxia of speech. These results warrant further investigation of the neural basis of childhood apraxia of speech, as well as the effects of TEMPO in inducing experience-dependent neural plasticity in a larger sample.

LIST OF REFERENCES

Ames H. (2009). Neural Dynamics of Speech Perception and Production: From Speaker Normalization to Apraxia of Speech. Unpublished doctoral dissertation. USA: Boston University

H. Ackermann, A. Riecker. (2010). The contribution(s) of the insula to speech production: a review of the clinical and functional imaging literature Brain Struct. Funct., 214, pp.419-433

American Speech-Language-Hearing Association. (2007). *Childhood apraxia of speech* [Position statement]. Available from www. Asha.org/policy

Ackermann H, Riecker A, Mathiak K, Erb M, Grodd W, Wildgruber D. (2001). Rate-dependent activation of a prefrontal-insular-cerebellar network during passive listening to trains of click stimuli: an fMRI study. *Neuroreport*. 12(18):4087–4092.

Ballard, K.J, Halaki, M., Sowman, P.F., Kha, A., Daliri, A., Robin, D…Guenther, F. (2018). An investigation of compensation and adaptation to auditory perturbations in individuals with acquired apraxia of speech. *Frontiers in Human Neuroscience.* 12, 510 doi: 10.3389/fn-hum.2018.00510

Ballard, K. J., Maas, E., & Robin, D. A. (2007). Treating voicing control in apraxia of speech with variable practice. *Aphasiology, 21,* 1195-1217.

Ballard, K. J., Robin, D. A., McCabe, P., & McDonald, J. (2010). A treatment for dysprosody in childhood apraxia of speech. Journal of Speech, Language, and Hearing Research, 53, 1227-1245.

Ballard, K. J., Tourville, J. A., Robin, D. A. (2014). Behavioral, computational, and neuroimaging studies of acquired apraxia of speech. *Frontiers in Human Neuroscience,* 8, 892. doi: 10.3389/fnhum.2014.00892

Ballard, K.J., Wambaugh, J.L., Duffy, J.R., Layfield, C., Maas, E., Mauszycki, S., McNeil, M.R. (2015). Treatment for acquired apraxia of speech: a systematic review of intervention research between 2004 and 2012. *American Journal of Speech-Language Pathology.* 24 (2), 316-337. doi: 10.1044/2015_AJSLP-14-0118

Boersma, P., & Weenink, D. (2001). Praat 3.9.15 [Computer software]. Amsterdam, the Netherlands: Institute of Phonetic Sciences.

Carrigg, B., Baker, E., Parry, L., & Ballard, K. J. (2015). Persistent speech sound disorder in a 22-year-old male: Communication, educational, socio-emotional and vocational outcomes. *SIG 16 Perspectives on School-Based Issues,* 16, 37-49. Doi:10.1044/sbi16.2.37

Dehaene-Lambertz G, Dehaene S, Hertz-Pannier L (2002) Functional neuroimaging of speech perception in infants. Science 298:2013- 2015, doi: 10.1126/science.1077066, pmid:12471265

Dronkers, N.F. (1996). A new brain region for coordinating speech. *Nature*. 384(6605): 159-161.

Duffy, J. R. (2013). *Motor speech disorders: Substrates, differential diagnosis, and management.* St. Louis, MO: Elsevier-Mosby.

Emerson R. W., Gao W., Lin W. (2016). Longitudinal Study of the Emerging Functional Connectivity Asymmetry of Primary Language Regions during Infancy. *Journal of Neuroscience*. 36 (42) 10883-10892. doi: 10.1523/JNEUROSCI.3980-15.2016

Graff-Radford J., Jones D.T., Strand E.A., Rabinstein A.A., Duffy J.R., Josephs K.A. (2014). The neuroanatomy of pure apraxia of speech in stroke. Brain Lang. 129:43–46.

Guenther F. H. (2006). Cortical interactions underlying the production of speech sounds. J. Commun. Disord. 39, 350–365. 10.1016/j.jcomdis.2006.06.013

Guenther F. H., Ghosh S. S., Tourville J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. Brain Lang. 96, 280–301. 10.1016/j.bandl.2005.06.001

Guenther, F. H., Hampson, M., & Johnson, D. (1998). A theoretical investigation of reference frames for the planning of speech movements. *Psychological Review, 105*(4), 611-633.

Guenther, F. H., Vladusich, T. (2012). A neural theory of speech acquisition and production. *Journal of Neurolinguistics*. 25 (5), 408-422. doi:10.1016/j.jneuroling.2009.08.006

Hillis A.E., Work M., Barker P.B., Jacobs M.A., Breese E.L., Maurer K. (2004). Re-examining the brain regions crucial for orchestrating speech articulation. Brain. 127(7):1479–1487.

Kent, R. D., & Read, C. (1992). *The acoustic analysis of speech.* San Diego, CA: Singular.

Klapp, S.T. (1995). Motor response programming during simple and choice reaction time: The role of practice. *Journal of Experimental Psychology: Human Perception and Performance, 21(5)*, 1015-1027.

Klapp, S.T. (2003). Reaction time analysis of two types of motor preparation for speech articulation: Action as a sequence of chunks. *Journal of Motor Behavior, 35(2)*, 135-150.

Kleim, J. A. & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing research, 51,* S225-S239.

Lewis, B.A., Freebairn, L.A., Hansen, A.J., Iyengar, S.K., Taylor, H.G. (2004). School-age follow-up of children with childhood apraxia of speech. anguage, Speech, and Hearing Services in Schools, 35 (2) 122-140.

Liegeois, F., Mayes, A., Morgan, A. (2014). Neural Correlates of Developmental Speech and Language Disorders: Evidence from Neuroimaging. *Current Developmental Disorders Reports.* 1 (3), 215-227.

Liegeois, F., Morgan, A. (2012). Neural bases of childhood speech disorders: Lateralization and plasticity for speech functions during development. *Neuroscience & Behavioral Reviews*. Vol. 36 (1), 439-458. doi: 10.1016/j.neubiorev.2011.07.011

Low, E.L., Grabe, E. & Nolan, F. (2000) Quantitative characterizations of speech rhythm: 'syllable-timing' in Singapore English. *Language and Speech*, in press, to appear in autumn 2000.

Ludlow, C. L., Hoit, J., Kent, R., Ramig, L. O., Shrivastav, R., Strand E., …Sapienza C. M. (2008). Translating principles of neural plasticity into research on speech motor control recovery and rehabilitation. *Journal of Speech, Language, and Hearing Research, 51*, S240-S258.

Maas, E., Mailend, M., Guenther, F. Feedfoward and Feedback Control in Apraxia of Speech: Effects of Noise Masking on Vowel Production. (2015). *Journal of Speech, Language, and Hearing Research.* 58 (2), 185-200. Doi: 10.1044/2014_JSLHR-S-13-300

Maas, E., Robin, D. A., Austermann Hula, S. N., Freedman, S. E., Wulf, G., Ballard, K. J., & Schmidt, R. A. (2008). Principles of motor learning in treatment of motor speech disorders. *American Journal of Speech-Language Pathology*, 17, 277-298. doi:10.1044/1058-0360(2008/025).

Maas, E., Robin, D., Steinhauer, V., Magnuson, C., Wright, D., and Ballard, K. (2006) *Apraxia of Speech as an Impairment of Preprogramming.* [Clinical Aphasiology Paper]

Maas, E., Robin, D. A., Wright, D. L., Ballard, K. J. (2008). Motor programming in apraxia of speech. Brain & Language, 106, 107-118.

Manes, J. & Robin, D. A. (2012). A motor learning perspective for optimizing treatment intensity. *International Journal of Speech-Language Pathology,* 14 (*5*), 447-450. doi:10.3109-17549507.2012.687399

McCabe, P., Murray, E., Thomas, D., & Evans, P. (2017). *Clinician Manual for Rapid Syllable Transition Treatment.* The University of Sydney, Camperdown, Australia.

McNeil M.R. (2011). Clinical Management of Sensorimotor Speech Disorders. Thieme; New York.

McNeil, M. R., Robin, D. A., & Schmidt, R. A. (2009). Apraxia of speech: Definition and differential diagnosis. In M. R. McNeil (Ed.), *Clinical management of sensorimotor speech disorders* (pp. 249-268). New York, NY: Thieme.

Miller, H (2018). Improvements in Speech of Children with Apraxia: The Efficacy of a Treatment for Establishing Motor Program Organization (TEMPO). (Unpublished Master's Thesis).

Murray, E., McCabe, P., & Ballard, K. J. (2014). A systematic review of treatment outcomes for children with childhood apraxia of speech. *American Journal of Speech-Language Pathology*, 23, 486-504. doi: 10.1044/2014_AJSLP-13-0035

Murray, E., McCabe, P., & Ballard, K. J. (2015). A randomized controlled trial for children with childhood apraxia of speech comparing Rapid Syllable Transition treatment and the Nuffield Dyspraxia Programme- Third Edition. *Journal of Speech, Language, and Hearing Research,* 58, 669-686. doi:10.1044/2015_JSLHR-S-13-0179.

Murray, E., McCabe, P., Heard, P., & Ballard, K. J. (2015). Differential diagnosis of children with suspected childhood apraxia of speech. *Journal of Speech, Language, and Hearing Research,* 58, 43-60. doi:10.1044/2014_JSLHR-S-12-0358.

Myers, EB, Blumstein, SE, Walsh, E and Eliassen, J (2009). Inferior frontal regions underlie the perception of phonetic category invariance. *Psychol Sci*, 20, 895–903.

New, A.B., Robin, D., Parkinson, A., Eickhoff, C., Kathrin, R., Hoffstaedter, F., …, Eickhoff, S. (2015). The intrinsic resting state voice network in Parkinson's disease: Intrinsic Voice Network in Parkinson's Disease. *Human Brain Mappings*, 36(5). doi: 10.1002/hbm.22748

New, A. B., Robin, D., Parkinson, A., Duffy, J., McNeil, M., Piguet, O., …, Ballard, K. (2015). Altered Resting-State Network Connectivity in Stroke Patients with and without Apraxia of Speech. *Neuroimage Clinical,* 8, 429-439. doi: 10.1016/j.nicl.2015.03.013

Nielsen J.M. Agnosia, Apraia, Aphasia: Their Value in Cerebral Localization. (1936). Hafner Company, Inc; New York.

Ogar J., Willock S., Baldo J., Wilkins D., Ludy C., Dronkers N. (2006). Clinical and anatomical correlates of apraxia of speech. Brain Lang. 97(3):343–350.

Oh, A., Duerden, E. G., & Pang, E. W. (2014). The role of the insula in speech and language processing. *Brain and language*, *135*, 96–103. doi:10.1016/j.bandl.2014.06.003

Perani D. Saccuman MC., Scifo P., Anwander A., Awander A., Spada D., Baldoli C., Poloniato A., Lohmann G., Friederici AD. (2011) Neural language networks at birth. Proc Natl Acad Sci U S A 108:16056–16061, doi:10.1073/pnas.1102991108, pmid:21896765.

Robin D.A., Jack A., Ramage A.E. (2008). The neural substrates of apraxia of speech as uncovered by brain imaging: A critical review. In: Ingham R.J., editor. Neuroimaging in communication sciences and disorders. Plural Publishing; San Diego. pp. 129–154.

Sato H., Hirabayashi Y., Tsubokura H., Kanai M., Ashida T., Konishi I., Uchida-Ota M., Konishi Y., Maki A. (2012) Cerebral hemodynamics in newborn infants exposed to speech sounds: a whole-head optical topography study. Hum Brain Mapp **33**:2092–2103, doi:10.1002/hbm.21350, pmid:21714036

Saur, D., Lange, R., Baumgärtner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain: a journal of neurology, 129 Pt 6*, 1371-84.

Schmidt, R. A. (1975). Schema theory of discrete motor skill learning. *Psychological Review, 82*, 225-260.

Schmidt, R. & Lee, T. (2005) *Motor control and learning: A behavioral emphasis* (4th ed.). Champaign, IL: Human Kinetics.

Shriberg, L.D., Lohmeier, H.L., Strand, E.A, Jakeilski, K.J. (2012). Encoding, memory, and transcoding deficits in Childhood Apraxia of Speech. *Clinical Linguistics and Phonetics*. 26 (5): 445-482. Doi: 3109/02699206.2012.655841

Shultz S., Vouloumanos A., Bennett R.H., Pelphrey K. (2014) Neural specialization for speech in the first months of life. Dev Sci 17:766- 774, doi:10.1111/desc.12151, pmid:24576182.

Smith, S.M.., Miller, K.L., Salimi-Khorshidi, G., Webster, M., Beckmann, C.F., Nichols, T.E.…Woolrich, M.W. (2011). "Network Modelling Methods for fMRI." *NeuroImage*, vol. 54, no. 2, 875-891, doi: 10.1016/j.neuroimage.2010.08.063

Strand, E. A., Stoeckel, R. & Baas, B. (2006). Treatment of severe childhood apraxia of speech: A treatment efficacy study. *Journal of Medical Speech-Language Pathology, 14*, 297-307.

Tourville J. T., Guenther F. H. (2011). The DIVA model: a neural theory of speech acquisition and production. Lang. Cogn. Proc. 25, 952–981. 10.1080/01690960903498424

H. Terband, B. Maassen, F.H. Guenther, J.Brumberg. (2009). Computational neural modeling of childhood apraxia of speech (CAS) J. Speech Lang. Hear Res., 52, pp. 1595-1609

Trupe L.A., Varma D.D., Gomez Y., Race D., Leigh R., Hillis A.E., Gottesman R.F. (2013). Chronic apraxia of speech and Broca's area. Stroke. 44(3):740–744.

Van den Heuvel M.P., Hulshoff Pol H.E. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur. Neuropsychopharmacol. 20(8):519–534.

Wertz R.T., LaPointe L.L., Rosenbek J.C. Apraxia of Speech in Adults: The Disorder and Its Management. (1984). Grune & Stratton; Orlando

Wiig, E. H., Semel, E., & Secord, W. A. (2013). Clinical Evaluation of Language Fundamentals, Fifth Edition (CELF-5). Bloomington, MN: NCS Pearson.

Ziegler, J.C., Castel, C., Pech-Georgel, C., George, F., Alario, F., Perry, C. (2008). Developmental dyslexia and the dual route of model reading: simulating individual differences and subtypes. *Cognition.*107 (1) 151-178. doi: 10.1016/j.cognition.2007.09/004

APPENDIX B: INSTITUTIONAL REVIEW BOARD APPROVAL

University *of* New Hampshire

Research Integrity Services, Service Building
51 College Road, Durham, NH 03824-3585
Fax: 603-862-3564

13-Jul-2017

Robin, Donald A
Communications Science Disorders, Hewitt Hall Rm 153
Durham, NH 03824-3520

IRB #: 6627
Study: TEMPO Treatment Study
Approval Expiration Date: 04-Apr-2018
Modification Approval Date: 10-Jul-2017
Modification: Mod #3: Addition of MRI for Children

The Institutional Review Board for the Protection of Human Subjects in Research (IRB) has reviewed and approved your modification to this study, as indicated above. Further changes in your study must be submitted to the IRB for review and approval prior to implementation.

Approval for this protocol expires on the date indicated above. At the end of the approval period you will be asked to submit a report with regard to the involvement of human subjects in this study. If your study is still active, you may request an extension of IRB approval.

Researchers who conduct studies involving human subjects have responsibilities as outlined in the document, *Responsibilities of Directors of Research Studies Involving Human Subjects.* This document is available at http://unh.edu/research/irb-application-resources or from me.

If you have questions or concerns about your study or this approval, please feel free to contact me at 603-862-2003 or Julie.simpson@unh.edu. Please refer to the IRB # above in all correspondence related to this study. The IRB wishes you success with your research.

For the IRB,

Julie F. Simpson
Director